

it was shown earlier that specific immunoglobulin G antibodies to parvovirus B19 are found in the majority of essential mixed cryoglobulinemia cases, and that parvovirus infection is rather not implicated in the pathogenesis of mixed cryoglobulinemia.<sup>4</sup> After all, the clinical syndrome in this case could be rather attributed to cryoglobulinemia itself. In this context, we believe that the title, as well as several points within the paper trying to associate the glomerulonephritis with a presumed acute parvovirus infection, might cause confusion to the reader. *In situ* hybridization in the renal tissue could provide more solid evidence regarding the probable causal relation between the infection and cryoglobulinemic glomerulonephritis.

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4. Cacoub P, Boukli N, Hausfater P *et al.* Parvovirus B19 infection, hepatitis C virus infection, and mixed cryoglobulinaemia. *Ann Rheum Dis* 1998; **57**: 422–424.

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**The Authors Reply:** In their letter, Drs Kirmizis and Chatzidimitriou<sup>1</sup> highlight the difficulties in ascribing causality for immune-mediated disease to an infectious agent. We agree that there is no evidence that in the case we described the cryoglobulin was secondary to acute parvovirus infection, but it was most likely a coincidental infection.<sup>2</sup> We are

confident that this was an acute infection as, unlike the previous cases of anti-parvovirus IgG positivity in patients with cryoglobulinemia,<sup>3</sup> we confirmed infection by performing parvovirus quantitative PCR that showed viral DNA in the patient's blood. Indeed this is why we investigated the cryoprecipitate and showed that there was no increased anti-parvovirus activity in the cryoprecipitate compared to the serum.

The title of our article sought to highlight the fact that the case was not secondary to hepatitis C or B infection and may have better been entitled 'non-viral hepatitis-associated cryoglobulinemia'. In addition to our findings, data from other centers suggest that in Northern European populations mixed essential cryoglobulinemia is often not associated with hepatitis C or B viral infections, in contrast to cases from Southern Europe.<sup>4</sup> Unlike parvovirus B19, hepatitis C virus is capable of exerting a direct effect on B lymphocytes, lending a pathophysiological link to the production of cryoglobulins. The reason for the discrepancies in viral etiology between different populations is interesting and we believe merits further investigation, which may ultimately lead to the discovery of another B-cell tropic cryoglobulin-inducing stimulus.

1. Kirmizis DA, Chatzidimitriou DA. Comment on "Non-hepatitis virus-associated mixed essential cryoglobulinemia". *Kidney Int* 2010; **78**: 113–114.
2. Annear NM, Cook HT, Atkins M *et al.* Non-hepatitis virus associated mixed essential cryoglobulinemia. *Kidney Int* 2010; **77**: 161–164.
3. Cacoub P, Boukli N, Hausfater P *et al.* Parvovirus B19 infection, hepatitis C virus infection, and mixed cryoglobulinaemia. *Ann Rheum Dis* 1998; **57**: 422–424.
4. Cohen Tervaert JW, Van Paassen P, Damoiseaux J. Type II cryoglobulinemia is not associated with hepatitis C infection: the Dutch experience. *Ann N Y Acad Sci* 2007; **1107**: 251–258.

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